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Quantum Mechanics/Molecular Mechanics (QM/MM) simulations: A modeling tool for Biomedicine and Biotechnology

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Molecular knowledge of enzyme-ligand complexes is crucial to understand their reactivity and thus design small molecules/protein mutations able to inhibit/modify enzyme activity. Complementing data science and other modeling approaches, Quantum Mechanics/Molecular Mechanics (QM/MM) simulations can provide further information on the enzymatic mechanism, thus facilitating such biomedical and biotechnological applications.

Here we exemplify this approach using as test case the unknown human gut bacterium mannoside phosphorylase (UhgbMP). Such enzyme is involved in the metabolization of eukaryotic N-glycans lining the intestinal epithelium, a factor associated with the onset and symptoms of inflammatory bowel disease. In addition, UhbgMP has been investigated for its potential to synthesize N-glycan core oligosaccharides very efficiently and less costly than by chemical means.

Using QM/MM simulations [1] we showed that the phosphorolysis reaction catalyzed by UhgbMP follows a novel substrate-assisted mechanism, in which the 3' hydroxyl group of the mannosyl unit of the substrate acts as a proton relay between the catalytic Asp104 and the glycosidic oxygen atom. Given the crucial role of the active site hydrogen bond network in the reaction and its conservation across mannoside-phosphorylases, the computed mechanism is expected to apply to other closely related enzyme families. Moreover, our simulations unraveled the conformational itinerary followed by the substrate along the reaction; such information can be used to design enzyme inhibitors. Future QM/MM simulations on the reverse phosphorolysis reaction also catalyzed by UhgbMP will provide hints to design protein mutations aiming at improving the biosynthetic yield of high added value products.

[1] https://doi.org/10.1021/acscatal.3c00451

Consent

Yes

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